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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/043,877
Filing Date: January 09, 2002
Appellant(s): MUKHOPADHYAY ET AL.

Tamara A. Kale
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 12/08/2006 appealing from the Office action mailed 7/10/2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

US 6,262,093	Camden	7-2001
US 5,880,144	Camden	3-1999

Perdomo et al., J. Cancer Res. Clin. Oncol., 124: 10-18, 1998

Delatour et al., Therapei, 31: 505-515, 1976

Nasr et al., J. Pharm. Sci., 74: 831-836, 1985

Lucci et al., Cancer, 86: 300-311, 2000

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

(A) Claims 76, 83-97 and 99-106 are rejected under 35 U.S.C. 103(a) as being unpatentable over Camden (US 6,262,093, 1999) in view of Perdomo *et al.* (J. Cancer Res. Clin. Oncol. 1998, 124, 10-18).

Camden teaches (column 11, line 69 to column 12, line 51) a method of inducing apoptosis in cancer cells expressing abnormal p53 by administering an effective amount of a benzimidazole derivative. The patent further teaches (column 12, line 52 to column 13, line 24) a method of treating a patient having cancer expressing abnormal p53 by administering an effective amount of a benzimidazole derivative to induce apoptosis. Moreover, Camden discloses (column 14, line 53 to column 24, line 31) a method of treating a patient with cancer comprising administering an effective amount of a benzimidazole derivative. With regards to the cancer, the patent teaches that cancer includes, but is not limited to, cancers of the breast, lung, non-small cell lung and sarcoma (column 3, lines 45-50) or cancer that has survived treatment with another anticancer agent (column 29, lines 9-13). Specifically, Camden discloses the apoptotic effect in cancer cells such as, for example, MCF7 breast cells both in vitro (column 12, lines 46-51) and in vivo (column 16, lines 48+). With regards to the cancer cells, the patent teaches (column 12, lines 46-51) that some of the cancer cell lines tested are known to express abnormal p53. With regards to administration, Camden provides that 1 to 1000 mg/kg of a benzimidazole derivative (column 5, line 58 to column 6, line 17) can be administered orally, by intravenous injection, by parental administration or by injection into or around the tumor (column 6, lines 26-43). In addition, Camden teaches that the compound can be

administered as a single daily dose or repeated at least once (column 6, lines 18-25). Furthermore, the patent shows that even at a concentration less than 10 μg/mL, the benzimidazole derivatives were capable of inducing apoptosis in p53 abnormal cell lines (column 12, lines 46-51). Thus, it does not appear that the claim language or limitation results in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

Camden does not teach determining the tumor suppressor status as recited in step (1), nor does Camden teach that the tumor suppressor status was determined by by way of Southern blotting, Northern blotting, PCR, ELISA or Western blotting (claims 23-28 and 101-106).

Perdomo *et al.* teach determining the p53 status, by Western blot analysis (page 12, 3rd paragraph) or other methods such as polymerase chain reaction (PCR), could make it possible to predict the response to therapy in certain patients (page 17, 1st column, 2nd paragraph). Perdomo *et al.* further teach that the response to cisplatin *in vivo* of NSCLC tumor lines was dependent on p53 status (page 17, 1st column, 2nd paragraph). Specifically, the reference teaches wt-p53 tumors showed a regression in size of around 60%, whereas mt-p53 tumors stopped growing (page 17, 1st column, 2nd paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to determine the status of a tumor suppressor gene, like p53, in a tumor cell prior to administering a benzimidazole derivative using techniques such as Western blot, PCR or other methods of analysis. One would have been motivated to do so because Camden teaches the selectivity in killing p53 abnormal cell lines versus cells expressing normal p53 (column 12, lines 52+), while Perdomo *et al.* teaches that the "response to cisplatin *in vivo* of tumors derived from different NSCLC lines was dependent on p53 status (page 17, 1st column, 2nd paragraph)." Further, one of ordinary skill in the art would have a reasonable expectation of success because Perdomo *et al.* teaches "analysis of p53 status, by immunohistochemical or other methods such as the polymerase chain reaction *(PCR)*, could make it possible to predict the response to therapy in certain patients (page 17, 1st column, 2nd paragraph)."

(B) Claims 76-77, 83-97, 99-106 are rejected under 35 U.S.C. 103(a) as being unpatentable over Camden (US 6,262,093, 1999) in view of Perdomo *et al.* (J. Cancer Res. Clin. Oncol. 1998, 124, 10-18) in further view of Delatour *et al.* (IDS, Therapie 1976; 31 (4); 505-515).

Camden in view of Perdomo et al. teach, as applied to claims 76, 83-97 and 99-106 above, method of treating cancer by inducing apoptosis to a cell expressing abnormal p53 comprising administering a benzimidazole derivative. Moreover, the combination teaches determining the p53 status prior to the administration of a benzimidazole derivative.

Camden in view of Perdomo et al. does not teach that the benzimidazole derivative is mebendazole.

Delatour *et al.* teach the ebryotoxic and antimitotic properties of benzimidazole compounds (title). Specifically, the reference discloses that in mice with Ehrich carcinoma mebendazole inhibited tumor growth and increased survival time (abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include mebendazole as taught by Delatour *et al.* in the method taught by Camden in view of Perdomo. One would have been motivated to make these modifications because as evidenced by Delatour *et al.*, benzimidazole derivatives such as mebendazole have been shown to inhibit tumor growth. Thus, one of ordinary skill in the art would have a reasonable expectation of success that using mebenzdazole as taught by Delatour *et al* in the method taught by Camden in view of Perdomo, one would achieve an additional benzimidazole derivative that induces apoptosis in cells and tumors expressing abnormal p53.

(C) Claims 2, 10, 15-19, 21-29, 76, 83, 85, 88-97 and 100-106 are rejected under 35 U.S.C. 103(a) as being unpatentable over Camden (US 5,880,144, 1999) as evidenced by Camden (US Patent 6,262,093, 1999) in view of Perdomo et al. (J. Cancer Res. Clin. Oncol. 1998, 124, 10-18) *of record.*

Camden teaches a method of killing lung tumor cells (A-549), breast tumor cells (MCF-7) and colon tumor cells comprising administering a benzimidazole derivative (column 6, lines 64 to 67, and column 7, Table 3). The patent further teaches a method of treating a patient having cancer comprising administering an effective amount of a benzimidazole derivative to inhibit the growth of the cancer (abstract). With regards to administration, Camden teaches (column 5, lines 1-10) that

the benzimidazole derivatives can be administered orally, by intravenous injection, by parental administration or by injection into or around the tumor. Although Camden does not specifically teach that the administration of benzimidazole induces apoptosis, the claimed functional limitation would be an inherent property of the referenced method because as evidenced by Camden (US Patent 6,262,093, 1999), the administration of benzimidazole derivatives results in apoptosis (see column 11, line 65 to column 12, line 51). Thus, it does not appear that the claim language or limitation results in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). Moreover, while Camden does not explicitly characterize the tumor cell lines as expressing a tumor suppressor gene such as p53, the claimed functional limitation would be an inherent property of the referenced method since the specification discusses (page 64, Table 4) that A459 tumor cells express wild-type p53. Thus, it does not appear that the claim language or limitation results in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

Hence, even though the claims are drawn to a mechanism by caner cells are inhibited, the claimed method does not appear to distinguish over the prior art teaching of the same or nearly the same method. The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

Camden does not teach determining the tumor suppressor status by way of Southern blotting, Northern blotting, PCR, ELISA or Western blotting (claims 23-28 and 101-106).

Perdomo *et al.* teach determining the p53 status, by Western blot analysis (page 12, 3rd paragraph) or other methods such as polymerase chain reaction (PCR), could make it possible to predict the response to therapy in certain patients (page 17, 1st column, 2nd paragraph). Perdomo *et al.* further teach that the response to cisplatin *in vivo* of NSCLC tumor lines was dependent on p53 status (page 17, 1st column, 2nd paragraph). Specifically, the reference teaches wt-p53 tumors showed

a regression in size of around 60%, whereas mt-p53 tumors stopped growing (page 17, 1st column, 2nd paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to determine the status of a tumor suppressor gene, like p53, in a tumor cell prior to administering a benzimidazole derivative using techniques such as Western blot, PCR or other methods of analysis. One would have been motivated to do so because Camden teaches the selectivity in killing p53 abnormal cell lines versus cells expressing normal p53 (column 12, lines 52+), while Perdomo *et al.* teaches that the "response to cisplatin *in vivo* of tumors derived from different NSCLC lines was dependent on p53 status (page 17, 1st column, 2nd paragraph)." Further, one of ordinary skill in the art would have a reasonable expectation of success because Perdomo *et al.* teaches "analysis of p53 status, by immunohistochemical or other methods such as the polymerase chain reaction *(PCR)*, could make it possible to predict the response to therapy in certain patients (page 17, 1st column, 2nd paragraph)."

(D) Claims 3 and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Camden (US 5,880,144, 1999) in view of Perdomo et al. (J. Cancer Res. Clin. Oncol. 1998, 124, 10-18), as set forth above for claims 2, 10, 15-19, 21-29, 76, 83, 85, 88-97 and 100-106, in further view of either of Delatour *et al.* (IDS, Therapie 1976; 31 (4); 505-515) of record or Nasr *et al.* (Journal of Pharmaceutical Sciences 1985; 74: 831-836).

Camden in view of Perdomo et al. teach a method of killing lung tumor cells (A-549), breast tumor cells (MCF-7) and colon tumor cells comprising administering a benzimidazole derivative (column 6, lines 64 to 67, and column 7, Table 3). The patent further teaches a method of treating a patient having cancer comprising administering an effective amount of a benzimidazole derivative to inhibit the growth of the cancer (abstract). Moreover, the combination teaches determining the p53 status prior to the administration of a benzimidazole derivative.

Camden in view of Perdomo et al. does not teach that the benzimidazole derivative is mebendazole.

Delatour *et al.* teach the ebryotoxic and antimitotic properties of benzimidazole compounds (title). Specifically, the reference discloses that a method of inhibiting tumor growth in mice comprising administering the benzimidazole derivative, mebendazole (abstract).

Nasr *et al.* teach (page 831, paragraph bridging 1st column and 2nd) *in vivo* anticancer activity correlation of aromatic, aliphatic, and heterocyclic carbamates and their thio-isosters against both intraperitoneally implanted murine P-388 lymphocytic leukemia and L-1210 lymphoid leukemia. Specifically, the reference teaches anticancer activity of benzimidazole carbonates (page 834, Table VIII and page 835, 2nd column, 2nd full paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the references so as to inhibit tumor growth because each of the benzimidazole derivatives disclosed by the references have close structural similarities and similar utilities. In the instant case, the courts have held that "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." In re Payne, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). See In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963); In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991) (see in MPEP § 2144) for an extensive review of the case law pertaining to obviousness based on close

structural similarity of chemical compounds. See also MPEP § 2144.08, paragraph II.A.4.(c). Thus, one of skill in the art would have a reasonable expectation of success that by substituting a benzimidazole derivate as taught by Delatour et al. or Nasr et al. in the method of Camden in view of Perdomo et al., one would achieve a method of inhibiting the growth of cancer.

(E) Claims 13-14 and 86-87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Camden (US 5,880,144, 1999) in view of Perdomo et al. (J. Cancer Res. Clin. Oncol. 1998, 124, 10-18), as set forth above for claims 2, 10, 15-19, 21-29, 76, 83, 85, 88-97 and 100-106, in further view of Lucci et al. (Cancer; 86:300-311, published online on November 2000).

Camden in view of Perdomo et al. teach a method of killing lung tumor cells (A-549), breast tumor cells (MCF-7) and colon tumor cells comprising administering a benzimidazole derivative (column 6, lines 64 to 67, and column 7, Table 3). The patent further teaches a method of treating a patient having cancer comprising administering an effective amount of a benzimidazole derivative to inhibit the growth of the cancer (abstract). Moreover, the combination teaches determining the p53 status prior to the administration of a benzimidazole derivative.

Camden in view of Perdomo et al not teach that the tumor cell is a multidrug resistant tumor cell, wherein the tumor cell is a breast tumor cell.

Lucci et al. teach multidrug resistance modulators and doxorubicin synergize to elevate ceramide levels and elicit apoptosis in drug-resistant cancer cells, specifically drug resistant human breast cancer cells lines. Moreover, the reference teaches that multidrug resistance is a formidable roadblock to the effective treatment of cancer by conventional chemotherapy, wherein the resistance complicates treatment in many instances (page 300, 1st paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use a multidrug resistant cell line, such as a breast cancer cell, in the method taught by Camden in view of the teachings of Lucci et al. One would have been motivated to do so because as taught by Lucci, multidrug resistance is a formidable roadblock to the effective treatment of cancer by conventional chemotherapy, wherein the resistance complicates treatment in many instances. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering a benzimidazole derivative to multidrug resistant cell, one would achieve a method

of inhibiting tumor growth in a patient that has already become resistant to conventional chemotherapy.

(10) Response to Argument

A. In response to the rejection of claims 76, 83-97 and 99-106 under 35 U.S.C. 103(a) as being unpatentable over Camden (US 6,262,093, 1999) (referred to herein as Camden I) in view of Perdomo *et al.* (J. Cancer Res. Clin. Oncol. 1998, 124, 10-18), Appellants assert the following:

(i) Camden I is not available as prior art under 35 U.S.C. 102 (e) as Appellants have demonstrated conception and reduction to practice prior to the filing date of Camden I. Specifically, Appellants assert that this was demonstrated in the Second Declaration of Tapas Mukhopahyay, Sunil Chada, Abner Mhashilkar and Jack A. Roth Under 37 C.F.R. 1.131 (Exhibit 3), which was accepted by the Examiner, in the November 2005 Office action, as reduction to practice as it pertains to *in vitro* claims, e.g., claims 1-3, 9-10 and 12-29. Appellants further assert that a Third Declaration of Tapas Mukhopahyay, Sunil Chada, Abner Mhashilkar and Jack A. Roth Under 37 C.F.R. 1.131 (Exhibit 5) was submitted demonstrating a showing of facts of such character and weight as to establish conception prior to March 9, 1999, coupled with diligence in the reduction to practice of in vivo treatment of cancer. However, Appellants assert that the Examiner, instead of responding directly to the issue of the establishment of *in vivo* conception plus reduction to practice, argues that the "Camden reference is a U.S. Patent or U.S. Patent application publication of a pending or patented application that claims the rejected invention or an obvious variant." (July 10, 2006 Action, p. 2 (Exhibit 6). Thus, Appellants assert that it appears that the Examiner is contending that the Third Declaration of Tapas Mukhopahyay, Sunil Chada, Abner Mhashilkar and Jack A. Roth Under 37 C.F.R. 1.131 is inappropriate "when the reference is claiming the same patentable invention or an obvious variant". Hence, Appellants submit that in view of the current interference rules, the standard by which the Examiner's position would be proper is "two-way" unpatentability, which means that the claims at issue would need to be drawn to the same patentable subject matter as the Camden I claims, i.e., to interfere with the claims of those references. However, Appellants argue that the Examiner has failed to clearly set forth any analysis as to why he believes that the Third Declaration is not appropriate under 37 C.F.R. 1.131; and further, Appellants argue that there is no evidence of record to support the Examiners conclusion because the Examiner has not clearly set forth reasons for any rejection. Although not required to do so,

Appellants submit a side by side comparison of claims 1 and 12 of Camden I as compared to claims 22 and 100 of the present invention which Appellants contend shows that claims 1 and 12 of Camden I are distinct from claims 22 and 100 of the present invention. Specifically, Appellants assert that present claims 22 and 100 are distinct from claims 1 and 12 of Camden I because of the recitations of the cancer cells expressing a tumor suppressor gene and determining the tumor suppressor gene status in the present invention. As such, Appellants assert that the claims cannot be conflicting by definition and therefore, the claims of Camden I fail to anticipate Appellant's claims and vice versa. In addition to the claims of Camden I failing to anticipate Appellant's claims and vice versa, Appellants assert that the claims of Camden I fail to render Appellant's claims obvious and vice versa. In particular, Appellants assert that there is only one other reference cited-Perdomo-from which one could possibly derive the elements clearly missing from the Camden I claims. However, Appellants assert that Perdomo is merely being cited as teaching that determination of p53 status of cancer cells "could make it possible to predict the response to therapy [cisplatin] in certain patients" and does not cure the deficiencies of the primary reference. Moreover, Appellants argue that no discussion has been provided as to why one skill in the art would equate the relationship between p53 and cisplatin with the limitations of the present invention and therefore be motivated to combine the elements set forth in present claims 22 or 100. Furthermore, Appellants assert that the Examiner has failed to even discuss the other required prong of the "two-way" test, namely, whether the claims of Camden I were rendered obvious by Appellants' claims.

(ii) Even if Camden I was available as prior art, the combination of Camden I in view of Perdomo would not render the claimed invention obvious. For example, Appellants assert that the combination of Camden I in view of Perdomo does not teach or suggest all of the claim limitations. In particular, Appellants assert that the Examiner has not shown that Camden I teaches induction of apoptosis in a cell as a result of expression of a tumor suppressor gene and the administration of a benzimidazole, or inhibition of cancer as a result of expression of a tumor suppressor gene and the administration of a benzimidazole. Furthermore, Appellants argue that the Examiner has not shown where Perdomo pertains to or teaches benzimidazole administration. In addition, Appellants argue that the combination of Camden I in view of Perdomo provides no motivation to one of ordinary skill in the art to provide for the claimed inventions. For example, Appellants argue that Perdomo states that "treatment with Cisplatin and radiation did not reduce the size of mt-p53 tumors, while

wt-p53 tumors regressed by approximately 60%." (abstract) Conversely, Appellants argue that Camden I is said to teach selectivity killing p53 abnormal cell lines versus cells expressing normal p53. Therefore, Appellants assert that one of ordinary skill in the art would not have been motivated to use benzimidazole derivatives taught by Camden I to induce apoptosis or inhibit cancer after confirming that the calls are expressing the p53 gene. Rather, Appellants argue that it would seem that the combination of these references actually teaches away from the present invention.

In response to A(i), the Examiner agrees with Appellants review of the prosecution history pertaining to the Second and Third Declarations by Tapas Mukhopahyay, Sunil Chada, Abner Mhashilkar and Jack A. Roth Under 37 C.F.R. 1.131 (Exhibit 3 and Exhibit 5); and further, that the Examiner is contending that the Third Declaration of Tapas Mukhopahyay, Sunil Chada, Abner Mhashilkar and Jack A. Roth Under 37 C.F.R. 1.131 is inappropriate "when the reference is claiming the same patentable invention or an obvious variant". However, a careful review of MPEP does not appear to support Appellants statement that "the standard by which the Examiner's position would be proper is "two-way" unpatentability". For example, the Examiner recognizes that a "one-way" test should be applied unless all three of the following apply: (1) the examined application has an effective U.S. filing date before that of a potentially conflicting patent; (2) there is sufficient evidence of record that the claims could not have been filed in the same application; and (3) there is sufficient evidence of record that there was administrative delay on the part of the Office in the application being examined, see MPEP 804. Conversely, if all three of the criteria set forth above are met, a "two-way" test should be applied. In the instant case, the pending application does not have an effective U.S. filing date before that of that conflicting patent, the claim could not have been filed in the same application because they have a different inventive entity and/or assignee, and there is insufficient evidence of record that the there was administrative delay on the part of the Office in the application being examined. Thus, in view of the MPEP, a "one-way" test appears to be the appropriate standard. As such, Appellant's arguments pertaining to the Examiner's failure to discuss the "two-way" test have not been considered. Along the same lines, regarding Appellants assertions that the Examiner has not set forth any reasons of record, e.g., rejections, the Examiner recognizes that, as stated in the prior office action, an affidavit or declaration is inappropriate under 37 CFR

1.131(a) when the reference is claiming the same patentable invention or are obvious variants, see MPEP § 608 and 2306. If the reference and this application are not commonly owned, the reference can only be overcome by establishing priority of invention through interference proceedings. As such, it is the Board of Patent Appeals and Interferences who enters final judgment on questions of priority and patentability. Moreover, the Examiner recognizes that it is important to note that this is not a rejection and accordingly is not required, *per se*, to clearly set forth any analysis as stated by Appellants. In the instant case, it is the Examiner's opinion that a statement such as "the reference is claiming the same patentable invention or are obvious variants" is sufficient for said reasoning.

In response to A(ii) pertaining to what Camden I does not teach, the Examiner acknowledges that Camden I does not explicitly teach induction of apoptosis as a result of expression of a tumor suppressor gene and administration of a benzimidazole derivative. However, the Examiner recognizes that Camden I teaches a method of inducing apoptosis in cancer cells expressing abnormal p53 by administering an effective amount of a benzimidazole derivative. Thus, the active step of administering a benzimidazole derivative and the resultant induction of apoptosis are clearly taught by the prior art. The mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145. Along the same lines, regarding Appellants contention that the combination does not teach or suggest all of the claimed limitation, the Examiner recognizes that Appellants appear to be considering the references individually. However, the courts have held that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller, 642 F.2d 13, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, Camden I teaches a method of inducing apoptosis in cancer cells expressing abnormal p53 by administering an effective amount of a benzimidazole derivate, while Perdomo reasonably conveys a mean by which to measure p53 expression, as well the importance of p53 expression in therapeutic outcome. As such, Camden I in view of Perdomo clearly teach all of the claimed limitations. In response to Appellants argument that there is no suggestion to combine the references, the examiner recognizes that references cannot be arbitrarily

combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that an "express, written motivation to combine must appear in prior art references before a finding of obviousness." See Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1276, 69 USPQ2d 1686, 1690 (Fed. Cir. 2004). For example, motivation to combine prior art references may exist in the nature of the problem to be solved (Ruiz at 1276, 69 USPQ2d at 1690) or the knowledge of one of ordinary skill in the art (National Steel Car v. Canadian Pacific Railway Ltd., 357 F.3d 1319, 1338, 69 USPQ2d 1641, 1656 (Fed. Cir. 2004)). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In the instant case, the motivation to combine the references is suggested by Perdomo whom teaches that the analysis of p53 status could make it possible to predict the response to therapy in certain patients.

B. In response to the rejection of Claims 76-77, 83-97, 99-106 under 35 U.S.C. 103(a) as being unpatentable over Camden (US 6,262,093, 1999) (Camden I) in view of Perdomo *et al.* (J. Cancer Res. Clin. Oncol. 1998, 124, 10-18) in further view of Delatour *et al.* (IDS, Therapie 1976; 31 (4); 505-515), Appellants argue that, as described above, Camden I is not available as prior art; and further, there Camden I and Perdomo do not teach or suggest each limitation of the claimed invention. Moreover, Appellants argue that the inclusion of Delatour fails to cure this deficiency because Delatour does not include any information pertaining to the tumor suppressor genes or determining their status prior to the administration of benzimidazole. In addition, Appellants argue that Delatour does not teach or suggest inhibition of cancer as a result of expression of a tumor suppressor and the administration of a benzimidazole.

First, Appellants arguments pertaining to the combination of Camden I and Perdomo have been addressed by the Examiner above and have been incorporated herein. Secondly, while the Examiner concedes that Delatour does not teach any information pertaining to tumor suppressor genes or determining their status prior to the administration of benzimidazole, Appellants, as described above, appear to be considering the references individually. However, the courts have held that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller, 642 F.2d 13, 208 USPQ 871 (CCPA 1981); In

re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, the Examiner recognizes that Delatour teaches administration of a benzimidazole derivative referred to as mebendazole for the inhibition of tumor growth. As such, both Camden I and Delatour teach art recognized benzimidazole derivatives which have been shown individually to be effective at inhibiting tumor growth. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include mebendazole as taught by Delatour *et al.* in the method taught by Camden in view of Perdomo for the treatment of cancer.

C. In response to the rejection of claims 2, 10, 15-19, 21-29, 76, 83, 85, 88-97 and 100-106 under 35 U.S.C. 103(a) as being unpatentable over Camden (US 5,880,144, 1999) (referred to herein as Camden II) as evidenced by Camden (US Patent 6,262,093, 1999) (Camden I) in view of Perdomo et al. (J. Cancer Res. Clin. Oncol. 1998, 124, 10-18), Appellants note that Camden I is unavailable as prior art. Appellants further argue, as discussed above which has been incorporated into this section, the combination of Camden I and Perdomo does not teach or suggest each limitation of the claimed invention. Moreover, Appellants argue that Camden II does not teach that the administration of benzimidazole induce apoptosis and does not characterize the tumor cells as expressing a tumor suppressor gene such as p53. Furthermore, Appellants argue that the Examiner has not shown where Perdomo pertains to or teaches benzimidazole administration. In addition, Appellants argue that the combination of Camden II as evidenced by Camden I in view of Perdomo provides no motivation to one of ordinary skill in the art to provide for the claimed inventions. For example, Appellants argue that Perdomo states that "treatment with Cisplatin and radiation did not reduce the size of mt-p53 tumors, while wt-p53 tumors regressed by approximately 60%. (abstract) Conversely, Appellants argue that Camden I is said to teach selectivity in killing p53 abnormal cell lines versus cells expressing normal p53. Therefore, Appellants assert that one of ordinary skill in the art would not have been motivated to use benzimidazole derivatives taught by Camden I to induce apoptosis or inhibit cancer after confirming that the calls are expressing the p53 gene. Rather, Appellants argue that it would seem that the combination of these references actually teaches away from the present invention.

In response to Appellants arguments pertaining to Camden II not teaching that the benzimidazole derivative induces apoptosis, the Examiner recognizes that Camden II does not

explicitly teach that the benzimidazole derivative induces apoptosis. However, the Examiner recognizes that the claimed functional limitation would be an inherent property of the referenced method because as evidenced by Camden (US Patent 6,262,093, 1999), the administration of benzimidazole derivatives results in apoptosis (see column 11, line 65 to column 12, line 51). Hence, even though the claims are drawn to a mechanism by which tumor cells are killed, the claimed method does not appear to distinguish over the prior art teaching of the same or nearly the same method. In the instant case, the mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Moreover, pertaining Appellants arguments that the combination does not teach or suggest all of the claimed limitation, the Examiner recognizes that Appellants appear to be considering the references individually. However, the courts have held that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller, 642 F.2d 13, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, Camden II teaches a method of inducing apoptosis in cancer cells which abnormally express p53, as evidenced by the specification, by administering an effective amount of a benzimidazole derivate, while Perdomo reasonably conveys a mean by which to measure p53 expression, as well the importance of p53 expression in therapeutic outcome. As such, Camden II in view of Perdomo clearly teach all of the claimed limitations. In response to Appellants argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation lies within Perdomo whom teaches that the analysis of p53 status could make it possible to predict the response to therapy in certain patients.

D. In response to the rejection of claims 3 and 77 under 35 U.S.C. 103(a) as being unpatentable over Camden (US 5,880,144, 1999) (Camden II) in view of Perdomo et al. (J. Cancer

Res. Clin. Oncol. 1998, 124, 10-18), as applied above to claims 2, 10, 15-19, 21-29, 76, 83, 85, 88-97 and 100-106, in further view of either of Delatour *et al.* (IDS, Therapie 1976; 31 (4); 505-515) of record or Nasr *et al.* (Journal of Pharmaceutical Sciences 1985; 74: 831-836), Appellants argue that, as described above, the combination of Camden II and Perdomo does not teach or suggest each limitation of the claimed invention; and therefore, does not provide any motivation to combine the references. Moreover, Appellants argue that the inclusion of Delatour or Nasr fails to cure this deficiency because Delatour or Nasr does not include any information pertaining to the tumor suppressor genes or determining their status prior to the administration of benzimidazole. In addition, Appellants argue that the Examiner has not indicate why one would be motivated to check the status of tumor suppressor genes in a tumor prior to the administration of a microtubule disruptor in the same manner as one might check the status of tumor suppressor genes prior to the administration of a DNA damaging agent.

First, Appellants arguments pertaining to the combination of Camden II and Perdomo have been addressed by the Examiner above and have been incorporated herein. Secondly, while the Examiner concedes that neither Delatour nor Nasr teach any information pertaining to the tumor suppressor genes or determining their status prior to the administration of benzimidazole, Appellants, as described above, appear to be considering the references individually. However, the courts have held that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller, 642 F.2d 13, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, the Examiner recognizes that both Delatour and Nasr teach administration of a benzimidazole derivatives for the inhibition of tumor growth. As such, Camden II, Delatour and Nasr teach art recognized benzimidazole derivatives which have been shown individually to be effective at inhibiting tumor growth. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include mebendazole as taught by Delatour *et al.* or Nasr in the method taught by Camden II in view of Perdomo for the treatment of cancer. Regarding the Appellants assertions pertaining to Perdomo, the Examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that an "express, written

motivation to combine must appear in prior art references before a finding of obviousness." See Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1276, 69 USPQ2d 1686, 1690 (Fed. Cir. 2004). For example, motivation to combine prior art references may exist in the nature of the problem to be solved (Ruiz at 1276, 69 USPQ2d at 1690) or the knowledge of one of ordinary skill in the art (National Steel Car v. Canadian Pacific Railway Ltd., 357 F.3d 1319, 1338, 69 USPQ2d 1641, 1656 (Fed. Cir. 2004)). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In the instant case, Perdomo suggests to one versed in the art that measuring tumor suppressor status, by Western blot analysis (page 12, 3rd paragraph) or other methods such as polymerase chain reaction (PCR), could make it possible to predict the response to therapy in certain patients (page 17, 1st column, 2nd paragraph).

E. In response to the rejection of claims 13-14 and 86-87 under 35 U.S.C. 103(a) as being unpatentable over Camden (US 5,880,144, 1999) in view of Perdomo et al. (J. Cancer Res. Clin. Oncol. 1998, 124, 10-18), as applied above to claims 2, 10, 15-19, 21-29, 76, 83, 85, 88-97 and 100-106, in further view of Lucci et al. (Cancer; 86:300-311, published online on November 2000), Appellants argue, as discussed above and incorporated into this section, the Examiner has failed to establish a prima facie case of obviousness based on Camden II and Perdomo. Appellants further argue that Lucci does not cure the deficiencies of Camden II and Perdomo. Particularly, Appellants argue that the combination of Camden II, Perdomo and Lucci fail to teach or suggest determining the tumor suppressor status of a cancer cell prior to administration of a benzimidazole, or inhibition of cancer or induction of apoptosis as a result of the administration of a benzimidazole and the expression of a tumor suppressor. Moreover, Appellants argue that Lucci appears to only disclose non-conventional chemotherapeutic drugs which bind P-glycoprotein and does not appear to identity or mention benzimidazoles or tumor suppressor gene status. As such, Appellants argue that the Examiner has not shown how the administration of the non-conventional chemotherapeutic agents taught by Lucci would provide a person of ordinary skill in the art the requisite motivation to practice the claimed invention given the deficiencies of the combination of Camden and Perdomo.

First, Appellants arguments pertaining to the combination of Camden II and Perdomo have been addressed by the Examiner above and have been incorporated herein. Regarding Appellants

arguments pertaining to Lucci et al., the Examiner acknowledges and concedes that Lucci et al. does not identify or mention benzimidazole derivatives. However, the Examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that an "express, written motivation to combine must appear in prior art references before a finding of obviousness." See Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1276, 69 USPQ2d 1686, 1690 (Fed. Cir. 2004). For example, motivation to combine prior art references may exist in the nature of the problem to be solved (Ruiz at 1276, 69 USPQ2d at 1690) or the knowledge of one of ordinary skill in the art (National Steel Car v. Canadian Pacific Railway Ltd., 357 F.3d 1319, 1338, 69 USPQ2d 1641, 1656 (Fed. Cir. 2004)). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In the instant case, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use a multidrug resistant cell line, such as a breast cancer cell, in the method taught by Camden in view of Lucci et al.'s teachings to one versed in the art that multidrug resistance is a formidable roadblock to the effective treatment of cancer by conventional chemotherapy, wherein the resistance complicates treatment in many instances (page 300, 1st paragraph).

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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